MIXED INFECTIONS AND THEIR CONTROL

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INTRODUCTION

Massive trauma predisposes the patient to bacterial invasion and sepsis as a consequence of the catabolic influence of hypermetabolism and resulting immune deficiency.[1] Systemic infection is a common complication of multiple injury despite the availability of potent and specific antibiotics.[2]

Infections following trauma are due to opportunistic pathogens that originate from endogenous or exogenous sources. These pathogens, often present as mixed infections, depend on the body site traumatized, the nature and severity of the trauma, and the circumstances of the injury. These organisms are often of enteric origin, and include Pseudomonas aeruginosa, Staphylococcus aureus, Proteus sp., Escherichia coli, Klebsiella pneumoniae, Clostridium sp., and Candida albicans. Recent work has shown that anaerobic organisms can also participate in the infectious process.[3] The anaerobes most frequently recovered are anaerobic Gram-positive cocci and the Bacteroides fragilis group. Colonization patterns established by opportunistic pathogens are dynamic, and flora found in wounds shortly after admission may not be the same as those found several days later.

Whole-body irradiation is associated with fatal septicemia in animals.[4] Postirradiation infections can also occur in man. Lymphatic and other tissues from Japanaese patients dying from the effects of the atomic blasts at Hiroshima and Nagasaki frequently revealed microscopic bacterial colonies of both Gram-positive and Gram-negative bacteria in the tissues.[5] In some cases of accidental whole-body exposures, infection with enteric organisms also occurred and presumably added to the radiation syndrome.[4] When a combination of trauma and other injuries occur in conjuction with irradiation, the risk of developing a serious infection is increased. Following such combined injury,

the role of proper therapy with antimicrobial agents is of primary importance. Studies have shown that appropriate management of these infections can reduce the morbidity and mortality following combined injury.[6]

A factor that complicates management of trauma-induced infections is that most of them are polymicrobial, including multiple aerobic and anaerobic organisms. Furthermore, due to the depletion of the host immune defenses, bactericidal antibiotics are preferred, and synergistic combinations of agents producing bactericidal action should be used.

The complex microflora associated with pyogenic wound and soft tissue infections generally reflect the indigenous flora of the skin or adjacent mucous membranes of the oropharyngeal, gastrointestinal, or genital tracts. Necrotizing wound and soft tissue infections are particularly prone to develop in areas with tissue ischemia and lowered oxidation-reduction potential. Risk of infection is also great at anatomic sites regularly exposed to fecal or oral contamination.

WOUND AND SKIN INFECTIONS

Beta-hemolytic streptococcus and S. aureus, either alone or in combination, are usually the causative organisms in skin infections.[7] Wounds associated with foreign bodies can be infected with P. aeruginosa.[7] Also many wound and skin infections following trauma are caused by mixed flora that are endogenous in nature and act synergistically.

Crepitant cellulitis is an acute anaerobic infection of the soft tissue that is characterized by abundant connective tissue gas and minimal systemic toxicity. Clostridium perfringens or other clostridial specimens are generally present in these lesions.[8] Other organisms that can be involved are Bacteroides, Peptostreptococcus, and coliforms.[9] Necrotizing fascitis, a gangrenous lesion, is generally caused by a variety of organisms including beta-hemolytic streptococci, S. aureus, Gram-negative enteric organisms, Peptostreptococcus, Bacteroides, and Fusobacterium.[10] Gas gangrene is a rapidly progressive, life-threatening, toxemia due to Clostridium infection of

muscle. It usually follows contamination of severe crushing muscle injury by animal or human feces.[1] C. perfringens or other clostridial species are isolated from most of the cases, sometimes mixed with other anaerobes and facultative organisms. Synergistic necrotizing gangrene is caused by the combination of (a) a microaerophilic nonhemolytic streptococcus, found primarily in the spreading periphery of the lesion, and (b) S. aureus in the zone of gangrene. A variety of other organisms can be seen instead of or in addition to the staphylococci. These include Proteus, Enterobacter, Pseudomonas, and Clostridium species.[11] Synergistic necrotizing cellulitis is caused by mixed infection containing one or more species of Gram-negative aerobic bacteria and at least one obligate anaerobe such as Bacteroides, Peptostreptococcus, or Peptococcus.[11]

Cutaneous abscesses are commonly encountered following wound infection, and can be caused by many aerobic and anaerobic pathogens. Although their treatment is usually surgical, knowledge of the usual flora causing infection in certain anatomic loci should permit the institution of therapy before the results of cultures are available. Anaerobes predominate in abscesses in the vulvo-vaginal, buttocks, perirectal, finger, and head areas, but aerobes are more prevalent in the neck, hand, leg, and trunk areas.[7] The major aerobes recovered are S. aureus, group A beta-hemolytic streptococci, Enterobacter, and E. coli. The common anaerobes recovered include anaerobic Gram-positive cocci, Bacteroides sp., and Fusobacterium sp.[7]

INFECTIONS FOLLOWING BLUNT TRAUMA

Microbial infection in impact and crushing injuries is of secondary importance to the original injury. In severe trauma, there may be multiple injuries to the head, chest, and abdomen as well as fractures of the extremities and crush injuries. The first concern is survival of the patient and maintaining vital functions. Frequently, severe injury is associated with impairment of host defense mechanisms, and the stage is set for subsequent serious infection. The two possible sources of microbial contamination at this time are the host and the environment.

The first and most common method of developing infection secondary to blunt trauma is a break in the mucosal barrier, which gives bacteria ready access to the peritoneal or pleural cavities. Bacteria from the patient's gastrointestinal and respiratory tracts may find egress from lacerations or disruptions of either tract. Rupture of any hollow viscus in the abdomen is followed by bacterial seeding of the peritoneal cavity.

Bacteria can also enter the tissues of the host and cause infection by secondary invasion.[8] A large hematoma, hemothorax, or any area of impaired blood supply is a favorable medium for the growth of endogenous microorganisms. Exogenous bacteria are usually not prime pathogens, and cause disease only if the local wound is not properly treated.[8]

INFECTIONS FOLLOWING PENETRATING INJURIES

Penetrating injuries occur in any part of the body. They are caused by a variety of agents, ranging from high-velocity bullets and shrapnel to knives and splinters. Many kinds of microorganisms cause infection following a penetrating injury. What is carried into the wound by the penetrating agent is important, as is the location of the wound and the organs that are perforated. Although almost any combination may occur, microorganisms from the gastrointestinal and respiratory tracts predominate.[7,8]

The wounding agent inevitably causes tissue destruction, usually introduces some foreign matter, and is associated with some degree of bleeding in the tract of penetration. This process establishes a culture medium suitable for microbial replication. With or without foreign matter, necrotic tissues and hematomas provide ideal conditions for growth: protection from phagocytes and humoral antibodies, depletion of oxygen and enhanced growth of microaerophilic and anaerobic microorganisms. When the penetrating wound enters the gastrointestinal tract, urinary tract, or respiratory tract, there is the serious complication of contamination by microorganisms resident in the host.

INTRAABDOMINAL INJURY

Secondary peritonitis and intraabdominal abscesses can be due to penetrating wounds. The infection is due to the entry of enteric microorganisms into the peritoneal cavity through a defect in the wall of the intestines or other viscus. The peritonitis following the rupture of a viscus is usually a synergistic infection. The specific microorganisms involved in peritonitis are generally those of the normal flora of the gastrointestinal tract where anaerobic bacteria outnumber aerobes in the ratio 1:1,000.[12] The presence of mixed aerobic and anaerobic flora in the peritoneal cavity was demonstrated in patients with ruptured viscus,[13] and these organisms were also recovered from the postoperative wound.[14]

Peritonitis is an excellent example of a synergistic infection between aerobic and anaerobic microorganisms. The two types of bacteria have opposite oxygen requirements, and the alteration that each causes in its environment as it grows permits the rapid proliferation of their partners.[10] The principal anaerobic pathogens are B. fragilis, Clostridium sp., and anaerobic Gram-positive cocci. Coliforms and facultative streptococci were frequent cohabitors.

BURN INFECTIONS

The most serious and common complication of burns is infection. A third-degree burn is more likely to be associated with severe infection than is a partial-thickness burn. Infection may be localized to the site of the burn or may be manifested as an overwhelming general sepsis. Burn wound sepsis is a major cause of death among burn patients.[15] Sepsis is characterized by progressive bacterial proliferation within the burned tissue, invasion into adjacent tissue, and systemic dissemination.[16]

Microorganisms usually gain access to burns directly from the skin. Soon after a burn injury, surface cultures may reveal multiple organisms. Within 3 to 5 days, the wound will become colonized by one or two specific organisms that have survived the competition with other microorganisms, or have proven

particularly resistant to burn wound therapy. The burn victim's diminished humoral and cellular defense systems make him more susceptible to infection. Deficiencies in the inflammatory response include diminished chemotaxis; diminished ability of the neutrophils to phagocytose and thereby kill offending bacteria; and a decrease in opsonin and antibody, which renders the bacteria susceptible to phagocytosis.

Streptococci were the principal burn pathogens in the past; currently S. aureus is much more commonly encountered. Gram-negative bacilli, especially P. aeruginosa, and fungi are also detected as the predominant pathogens in burn wounds. Anaerobes belonging to the Bacteroides and Fusobacterium sp. can be found in burns in the oral and anal areas.[17]

INFECTIONS FOLLOWING IRRADIATION

The severe hematological and gastrointestinal injury caused by irradiation makes the affected individual more susceptible to exogenous infections and to septicemia due to spread of his own indigenous flora. Most of the data in this field were obtained from studies done in animal models. However, much can be learned from the susceptibility to infections of individuals immunosuppressed by other means.

The predominant organisms causing sepsis following irradiation are E. coli, Proteus sp., P. aeruginosa, Enterococci, and S. aureus.[4] Anaerobic bacteria such as anaerobic Gram-positive cocci and B. fragilis are also recovered from irradiated animals.[3] The infections that develop in irradiated animals are generally polymicrobial due to mixed aerobic and/or anaerobic bacteria.[3,4]

BACTERIAL SYNERGISM

Polymicrobic infections are more pathogenic for experimental animals than are those involving single organisms.[18] The potential importance of synergy such as this was first emphasized by Altemeier who noted a direct correlation between peritonitis mortality rates and the number of bacterial species

cultivated from the peritoneal fluid.[19] Support for this thesis was provided by showing that intraperitoneal challenge with the isolates in pure culture was generally well tolerated by animals, but combinations of the various isolates produced rapid lethality.[20] A similar observation was noted by Meleney, who studied synergism between E. coli, C. perfringens, and a nonhemolytic streptococcus.[21]

McDonald et al. studied synergistic interaction between aerobes and anaerobes, and found that B. melaninogenicus was indispensable in producing abscesses following subcutaneous injections into animals.[22] However, it was necessary to include another microbe in the inoculum to provide a source of vitamin K_1, which is a growth requirement for B. melaninogenicus.[23] A similar mechanism of synergy is seen with foot rot in sheep, in which Fusobacterium necrophorum is the invading microbe, but its required growth factors are supplied by the concurrent presence of Corynebacterium.[24] This synergistic interaction is somewhat more complicated because F. necrophorum also protects its nutrient supply with the production of a leukocidin that prevents phagocytosis of the Corynebacterium.

Another mechanism of synergy was described by Meleney in his classical studies of synergistic bacterial gangrene.[25] He found that cultures from the central bed of the ulcer yielded S. aureus and a microaerophilic streptococcus, but cultures from the advancing edge of inflammation showed only the latter organism. This lesion could be reproduced in experimental animals only with an inoculum composed of both bacteria. Subsequent work indicated that the role of the S. aureus was to produce hyaluronidase, which promoted the invasive potential of the microaerophilic streptococcus.[26]

In recent studies we have demonstrated the ability of "helper" organisms, generally recovered mixed with anaerobes, to induce capsule formation in unencapsulated Bacteroides sp.[27] These Bacteroides sp. included strains of B. melaninogenicus and fragilis groups, B. oralis, and B. ruminocola ssp. brevis. The previously non-encapsulated Bacteroides species were non-pathogenic in vivo, and did not cause abscesses following their inoculation into animals. However, following their co-inoculation with abscess-forming organisms, they

acquired capsular material, and were thereafter able to cause abscesses by themselves. This phenomenon can be due to various yet-undetermined mechanisms. One could be due to *in vivo* transfer to DNA from encapsulated to unencapsulated organisms. An alternate explanation is that the presence of capsular material from the "helper" organism was sufficient to prevent phagocytosis of the organisms and permit the selection of encapsulated organisms. It is postulated that a selection process was the mechanism responsible for the phenomenon, due to the presence of a few encapsulated organisms in populations of the initially non-encapsulated strains. Selection *in vivo* of encapsulated *Bacteroides* sp., with the assistance of other encapsulated, or non-encapsulated but abscess-forming aerobic and anaerobic organisms, may explain the apparent conversion into pathogens of non-pathogenic organisms that are part of normal host flora. This phenomenon could contribute to the ability of *B. fragilis* (which constitutes only about 0.5% of the normal fecal flora) to become a pathogen present in 70% to 80% of intra-abdominal infections.

In other studies (unpublished data), we found synergy between anaerobic Gram-positive cocci and *Bacteroides* sp. or *Pseudomonas aeruginosa*. The number of bacteria required to cause lethality or abscess formation was reduced by 15-fold or more when a combination of microbes was used rather than single strains alone.

The experimental data presented demonstrate the important role of facultative bacteria in mixed aerobic and anaerobic infection. The mechanisms of their influence on the infectious process may include the promotion of an appropriate environment for anaerobic growth, the production of necessary nutrients, the production of extracellular enzymes to promote tissue invasion by the anaerobe, and assistance in selection of encapsulated strains.

MANAGEMENT OF INFECTIONS FOLLOWING TRAUMA AND IRRADIATION

The strategy for therapy of post-trauma infections includes surgical drainage of pus, debridement of any necrotic tissue, and appropriate use of antibiotics. Certain types of adjunctive therapy, such as hyperbaric oxygen, may also be useful.

Surgery may be the only therapy required in some cases, such as localized abscesses or decubitus ulcers without signs of systemic involvement. However, antibiotics are indicated in the majority of patients whenever systemic manifestations of infection are present or when suppuration either extends or threatens to spread into surrounding tissue. In many infections, antimicrobial therapy alone is sufficient; in others, it is an important adjunct to the surgical approach.

Selection of antimicrobial agents is simplified when results of culture from a reliable specimen are available. This is seldom the case, however, in infections involving anaerobes, and many patients are treated empirically on the basis of suspected rather than established pathogens. Fortunately, the types of bacteria involved in many infections and their antimicrobial susceptibility patterns tend to be predictable. However, some bacteria have become resistant to antimicrobial agents, and many can become resistant while a patient is receiving therapy.[28] Other factors may also influence the choice of antimicrobial therapy, e.g., pharmacologic characteristics of the various drugs, their toxicity, their effect on the normal flora, and bactericidal activity.[8]

ANTIMICROBIAL AGENTS

Since anaerobic bacteria mixed with aerobic organisms are generally recovered in many infections, the selection of proper therapy may become complicated. The choice of the appropriate antimicrobial agents, therefore, should provide adequate coverage for most of the pathogens recovered. Table 1 summarizes the antimicrobial agents effective against most organisms present in mixed infections.

PENICILLIN. This antibiotic is effective against aerobic streptococci and most anaerobic species except those that produce beta-lactamase, which are generally susceptible to penicillin. B. fragilis is resistant to penicillin[28] resistance to penicillin is also appearing in growing numbers of other Bacteroides species (e.g., B. melaninogenicus and B. oralis) as well as strains of Clostridium, Fusobacterium, and microaerophilic streptococci.

Methicillin, nafcillin, and the isoxazolyl penicillins (oxacillin, cloxacillin, and dicloxacillin) have excellent activity against S. aureus but have unpredictable activity against anaerobes and are frequently inferior to penicillin G.[8]

Antimicrobial Agent	Anaerobic bacteria		Aerobic bacteria	
	B. fragilis gr.	Other anaerobes	Gram-positive cocci	Enteric
Penicillin[a]	poor	excellent	good	poor
Chloramphenicol[a]	excellent	excellent	good	variable
Cepholothin*	poor	good	good	poor
Cefoxitin[b]*	excellent	excellent	good	good
Moxalactam[c]	excellent	excellent	good	good
Clindamicin*	excellent	excellent	very good	poor
Carbenicillin-ticarcillin[d]	good	excellent	good	very good
Metronidazole[e]	excellent	excellent	poor	poor

* = does not penetrate the central nervous system

[a] Poor for S. aureus

[b] Not effective against P. aeruginosa, Enterobacter sp., S. faecalis

[c] Not effective against enterococci, some strains of B. fragilis, P. aeruginosa

[d] Some centers have reported increased resistance; no activity against S. aureus or K. pneumoniae.

[e] Anaerobic Gram-positive bacilli may be resistant.

CARBENICILLIN AND TICARCILLIN. These penicillin derivatives have good in vitro activity against most strains of B. fragilis as well as other penicillin-sensitive anaerobes[28] and P. aeruginosa.

CEPHALOSPORINS. The antimicrobial spectrum of first - generation cephalosporins against anaerobes is similar to that of penicillin G, although they are less active per unit weight. Most strains of B. fragilis and many of B. melaninogenicus are resistant by virtue of cephalosporinase production[8,28]. Cefoxitin, a second-generation cephalosporin, is relatively resistant to this enzyme and is therefore effective against B. fragilis. The third-generation cephalosporins have a broad spectrum of activity against enteric Gram-negative bacilli and most strains of B. fragilis.[28]

CHLORAMPHENICOL. This drug is very active against anaerobes and many Gram-negative enteric organisms.[8,28] It is the drug of choice for treatment of anaerobic infections of the central nervous system.

CLINDAMYCIN. Clindamycin has a broad range of activity against anaerobic organisms, including B. fragilis, and is effective against S. aureus and streptococci. The primary manifestation of toxicity with clindamycin is colitis. It should be kept in mind that colitis has been associated with a number of other antimicrobial agents, such as ampicillin and many cephalosporins.

METRONIDAZOLE. This antibiotic has excellent in vitro activity against most obligate anaerobes, including B. fragilis.[28] Aerobic and faculative anaerobes, such as coliforms, are usually highly resistant.

AMINOGLYCOSIDES. This group of agents (gentamicin, amikacin tobramicin) are very effective against Gram-negative enteric aerobic bacteria, and they possess some activity against S. aureus. However, they are inactive against anaerobic bacteria. They manifest synergistic activity with penicillins against S. aureus, Group B streptococci, Listeria monocytogenes,[29] and B. melaninogenicus.[30]

CLAVULANIC ACID. Clavulanic acid is a beta-lactamase inhibitor that resembles the nucleus of penicillin. It irreversibly inhibits beta-lactamase enzymes produced by some enterobacteriaceae, staphylococci,[31] and Bacteroides species.[32] Clavulanic acid and other beta-lactamase inhibitors have very weak

antibacterial activity alone, but when used in conjunction with a beta-lactam antibiotic, they are effective in treating infections caused by beta lactamase-producing bacteria. Its usefulness in the chemotherapy of human infections is currently being evaluated.

SYNERGISTIC ANTIMICROBIAL COMBINATIONS

Combinations of antibiotics are continually being studied in attempts to discover more effective therapy for serious infections. Combined therapy might delay the emergence of antimicrobial resistance, provide broad-spectrum coverage for infections of unknown or mixed etiology, or generate a greater antibacterial effect against specific pathogens than is achievable with a single drug. The improved killing of the offending anaerobic organisms, as expressed by effective bactericidal activity, is especially important in the treatment of endocarditis, bacteremia, and closed-space infections, such as brain or lung abscesses that cannot be surgically drained.

Combination therapy should not be used indiscriminately, for two reasons. First, the risks of adverse reactions are increased when multiple drugs are administered. Second, combination therapy is sometimes less effective than a single drug against a specific pathogen.[29]

Synergistic interaction between aminoglycosides and penicillins against aerobic organisms has been observed. This combination is effective in the treatment of enterococcal and staphylococcal diseases. It is postulated that the penicillin, which inhibits bacterial cell wall synthesis, enhances the penetration of aminoglycosides, which have a lethal effect on the ribosomes. B. fragilis, a strict anaerobe, is resistant to aminoglycosides, because these agents are poorly transported into facultatively anaerobic bacteria under anaerobic conditions.[33] However, a recent study[34] demonstrated that the ribosomes of the strictly anaerobic bacteria C. perfringens and B. fragilis are susceptible to the action of streptomycin and gentamicin. The susceptibility of the Bacteroides ribosome to aminoglycosides, combined with the ability of penicillin to alter the organisms' membranes, suggests a possible explanation for the recently observed synergistic combination between the agents against B. melaninogenicus.[29]

BETA-LACTAMASE PRODUCTION

Many aerobic and anaerobic microorganisms, including B. fragilis, produce beta-lactamase, which enables them to resist penicillin.[35] Until recently, most B. melaninogenicus and B. oralis strains were considered susceptible to penicillin. However, within the past decade, penicillin-resistant strains have been reported with increasing frequency.[35]

The appearance of penicillin resistance among Bacteroides sp. has important implications for chemotherapy. These organisms may release beta-lactamase into the environment, thus degrading penicillin and protecting not only themselves but also other penicillin-sensitive pathogens. Therefore, penicillin therapy directed against a susceptible pathogen might be rendered ineffective by the presence of a penicillinase-producing organism.

Several studies demonstrate the activity of this enzyme in clinical infections. Louvois and Hurley demonstrated the degradation of penicillin, ampicillin, and cephaloridine by purulent exudates obtained from four of 22 patients with abscesses.[36] Beta-lactamase activity has also been found in empyema fluid[37] and in samples of pus obtained from 12 patients with polymicrobial intra-abdominal abscesses or polymicrobial empyema.[38]

The importance of beta-lactamase production in anaerobic infections was demonstrated by Hackman and Wilkins,[39] who were able to show that penicillin-resistant strains of B. fragilis, B. menaninogenicus, and B. oralis could protect F. necrophorum from penicillin therapy in mice. O'Keefe et al.[40] demonstrated inactivation of penicillin-G in an experimental B. fragilis infection model in the rabbit peritoneum.

We have recently demonstrated the ability of beta lactamase-producing B. fragilis and B. melaninogenicus to protect group A beta-hemolytic streptococci from penicillin in mice.[41] We also observed that the beta-lactamase produced by aerobic organisms (such as K. pneumoniae or S. aureus) had a protective effect on penicillin-susceptible B. melaninogenicus. Penicillin was ineffective

in eradicating the penicillin-susceptible anaerobe in the presence of the aerobic beta-lactamase producer; however, the combination of clavulanic acid and pencillin was effective.

The results of all of these studies raise questions concerning the efficacy of beta-lactamase-susceptible antibiotics against beta-lactamase-producing aerobic and anaerobic bacteria. In seriously ill patients with mixed infections where beta-lactamase-producing bacteria are present, administering antibiotics that are effective against these beta-lactamase producers should be considered. The recent development of potent enzyme inhibitors, such as clavulanic acid, may facilitate a new approach to this problem.

IMPORTANCE OF THERAPY OF ALL COMPONENTS OF MIXED INFECTION

The necessity for treating all components of mixed infections has now been adequately documented in both experimental and clinical studies. The importance of synergistic antimicrobial therapy that will be effective against both aerobic and anaerobic bacteria present in a mixed infection was demonstrated in animal models for treatment of intra-abdominal infection. Peritonitis was induced in rats by introducing gelatin capsules containing cecal contents into their abdominal cavities.[42] The animals that survived the initial septicemic stage caused by coliforms developed intra-abdominal abscesses caused by anaerobes. An evaluation of the effect of therapy with clindamycin, gentamicin, or a combination of both was done. It was shown that the untreated control group and the clindamycin-treated group had identical mortality rates of about 35% due to E. coli sepsis. However, administration of gentamicin alone or in combination with clindamycin led to greater than 90% survival. The data suggest that the early mortality in the peritonitis and septicemic phase is attributable to gentamicin-sensitive coliform bacteria. The effect of this treatment on abscess formation was entirely different. All untreated animals that survived developed abscesses due to B. fragilis, as did those treated with gentamicin alone. However, the use of clindamycin alone or in combination with gentamicin was associated with a greatly reduced incidence of abscesses from 100% to only 5%. These findings

indicate that anaerobes may be responsible for complications following abdominal perforation, such as intra-abdominal abscess formation, and show that optimal treatment of intestinal perforation requires a drug to control both aerobic and anaerobic bacteria.

Clinical work also supports these animal data. Thadepalli et al.[43] treated 100 patients with a perforated small or large intestine. Two regimens were used. Fifty-two patients received a cephalosporin-kanamycin combination and 48 received clindamycin plus kanamycin. Since both groups were provided with kanamycin activity against coliforms, the point of comparison was between cephalothin (poor antianaerobic activity) versus clindamycin (excellent antianaerobic activity). In the cephalothin group, 14 patients developed abscess, wound infection, or septicemia, compared with only 5 patients in the clindamycin group. Anaerobes, moreover, were involved in 11 episodes of septic complications in the patients receiving cephalothin but in only 1 episode in those receiving clindamycin. Many other studies have shown similar results. These studies demonstrate the need for directing therapy at the anaerobic component of mixed infections, in addition to the aerobic component, for optimal therapeutic results.

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DISCUSSION PERIOD WITH DR. BROOK

DR. VAN DER WAAIJ: Do you have an explanation for the transfer of the genetic information from perhaps the E. coli to the B. fragilis concerning the formation of capsule? Was it capsule conjugation or transformation?

DR. BROOK: We believe that it is a selection process. However, we don't have a complete explanation. We did find that some organisms among the groups that we called the non-encapsulated, in the early stages, before we injected them for the first time in mice, did have a capsule. There probably was a selection process for encapsulated bacteria in the animal.

If we did interrupt the experiment within less than 7 to 10 days, we couldn't find many encapsulated organisms. So it was not a phenomenon of all or none; it was a selection for a population that was encapsulated from the beginning.